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DISCOVERY

Cardiovascular and renal disease risk in relation to microalbuminuria in type 2 diabetes mellitus patients in Bangladeshi population

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ABSTRACT

Microalbuminuria is a strong and established risk marker for cardiovascular disease and progressive renal impairment in type 2 diabetes (T2D) patients. This study is an attempt to investigate the association of microalbuminuria with cardiovascular and kidney disease progression in type 2 diabetic patients in Bangladeshi population. A total of 149 participants with minimum of five years of type 2 diabetes mellitus were included in the study. Among them, 92 were normoalbuminuric and 57 were microalbuminuric patients and they were matched for age, BMI, duration of diabetes, blood pressure and blood glucose level. Their creatinine level and troponine I and ECG (Electrocardiogram) reports were recorded as the markers of renal and cardiovascular diseases. In this study, overall prevalence of microalbuminuria was found 38%.Pearson correlation of microalbuminuria with creatinine level showed statistically significant linear relationship that indicated association of microalbuminuria with chronic kidney disease. Moreover, the ANOVA result of Troponine I and ECG have shown positive correlation with microalbuminuria suggesting the association of microalbuminuria with clinical cardiovascular diseases. These findings reveal microalbuminuria as a sensitive marker for the susceptibility of type 2 diabetic patients to cardiovascular and renal diseases. However, additional studies using large sample size with very strict criteria of selection and judgment are needed to confirm the results.

Keywords: Cardiovascular risk, Creatinine, ECG, Microalbuminuria, Renal risk, Troponin I, Type 2 Diabetes (T2D).

1. INTRODUCTION

Diabetes mellitus (DM) has been marked as global health problem since it may lead to long term deleterious effects which include cardiovascular, renal and all other mortality. The global incidence of diabetes among adults is predicted to be rise to 13% by 2030 (Beilin *et al*, 1996). In Bangladesh, the rate will be increased substantially from 5.10 million to 8.2 million by 2035 as well (Hira *et al*, 2018). On the other hand, progressive increase in the excretion of protein, particularly albumin through the glomerular filtration barrier is reported to cause renal complications and cardiovascular diseases. In both type 1 and 2 DM, persistent elevation of albumin in the urine of >30 to <300 mg/d (>20 to <200 microg/min) or an albumin to creatinine ratio (mg/mmol) of 2.5 to 25 in males and 3.5 to 35 in females termed as microalbuminuria (Jerums and MacIsaac, 2002). In type-2 diabetes mellitus, the prevalence of microalbuminuria ranges from 8–47% (Naidoo, 2002). Now it is considered as an important clinical tool because of its close association with not only progression to overt proteinuria (also called macroalbuminuria, ranging of urinary albumin excretion (UAE) ≥300 mg/24 h) and renal failure, but also cardiovascular events. It has also been observed that by an interval of 5 to 10 years, microalbuminuria usually precedes macroalbuminuria in patients with diabetes. However, hypertension, cardiovascular disease and renal disease can still occur in the microalbuminuric range in diabetic patients.

Cardiovascular disease and coronary heart disease increases the risk of death in type 2 diabetic patients which is more than 75% in low and middle income countries (Beilin *et al*, 1996; Murthy *et al,* 2019). Strikingly urine microalbumin is one of the commonly recognized risk factors for CVD which is more prevalent in diabetic patients (Naha *et al*, 2015). In both type 1 and type 2 diabetes, this marker positively correlated with the presence of atherosclerotic risk factors and disease as well as hypertension, dyslipidaemia and insulin resistance etc (Beilin *et al*, 1996). Since the underlying mechanism of microalbuminuria with cardiovascular disease is still not clear, one possible reason could be the excess leak of albumin in both renal and systemic vessels. It may cause widespread endothelial dysfunction arises from the loss of systemic endothelial glycocaylx which may contribute to the pathogenesis of cardiovascular disease in diabetes mellitus (Naidoo, 2002). Under normal physiological conditions, a healthy endothelium releases endothelial-derived relaxing and contracting factors and inhibits platelet and leukocyte adhesion to the vascular surface, thus maintain vascular tone and structure. But in diabetes and atherosclerosis, changes of this delicate balance, contribute the progression of end-organ damage (Cosentino and Lüscher, 1998). In addition to, this endothelial dysfunction increases the penetration of atherogenic lipoprotein, apolipoprotein particles and atherosclerosis in the arterial wall that elevates the prevalence of cardiovascular mortality two or three times greater in the population (Beilin *et al*, 1996; Murthy *et al,* 2019).

It has been reported that cardiovascular risk progressively declines not only renal function but also increases the risk for hypertension as well as end stage renal disease (ESRD).In addition, increased urinary albumin excretion (UAE) has been identified as a precursor of overt kidney disease in patients with diabetes (Chin'ombe *et al,* 2013). It may alter the glomerular filtration barrier as well as glomerular permeability in persistent hyperglycemia. Reactive oxygen species, inflammatory cytokines and growth factors play major role in glomerular endothelial dysfunction which is the initiating step of chronic kidney disease (CKD) (Satchell and Tooke, 2008).The above changes expanse the glomerular capillaries which lead to the impairment of the filter function and loss of

proteins in the urine (Cravedi and Remuzzi, 2013). Thus the understanding of the pathophysiology of microalbuminuria will help to design therapies and decrease the mortality rate happened due to diabetes mellitus.

The majority of the diabetes mellitus patients belongs to type 2 diabetes mellitus. Microalbuminuria is an early predictor of cardiovascular disease and renal impairment in these patients. However, the association of microalbuminuria with hypertension, cardiovascular, and renal disease has been studied in only a few longitudinal studies but no strong evidence has found. Therefore, the aim of the present study was to examine the level of microalbuminuria in patients with minimum five (5) years of type 2 diabetes mellitus and determine the association of microalbuminuria with cardiovascular disease and kidney disease progression in Bangladeshi population.

2. MATERIALS AND METHODS

Study population

This cross sectional study was carried out among adult people who underwent a health checkup at Mitford Hospital, Dhaka. The final sample size included in this study was 149. The study had divided into two components to conduct the experiment. First, the prevalence of microalbuminuria was examined among all the patients of type 2 DM and the second part was to establish the association of microalbuminuria with renal and heart disease.

Anthropometric measurements

To accomplish the first part, 149 participants with minimum of five years of type 2 Diabetes Mellitus provided information by completing a standard self-administered questionnaire including their medical and family history, usage of medication, smoking status, alcohol intake, physical ability, and education status. All participants were explained about the nature of the study and written consent form was obtained. They were also informed about their rights to withdraw from the study at any time. Blood pressure and other anthropometric parameters were estimated by skilled staff members. The calculation of BMI (Body mass index) was expressed as weight in kilograms by dividing height in meters squared (kg/m^2) (Hong *et al,* 2017).

Diabetes related tests

Blood samples were collected for FBS (Fasting Blood Sugar), 2hrs. ABF (After Breakfast), RBS (Random blood sugar) & HbA1c (Glycolated hemoglobin) tests to detect diabetes mellitus by Automated Biochemistry Analyzer, Dimension EXL 200 (Siemens) (Ghazanfari *et al*, 2010).

Microalbumin test

To detect microalbuminuria in patients, at first urine sample was collected on spot. Then the test was performed by using "Getin 110 Immunofluorescence Quantitative Analyzer". The detection method is Immunofluorescence Assay (IFA) & the reference range of MAU is: < 10.0 (unit) (American Diabetes Association, 2004).

Renal function tests

In this study, serum creatinine was measured for detection of renal disorder using Automated Biochemistry Analyzer Dimension EXL 200 (Siemens) by enzymatic method (Moss *et al*, 1975).

Heart function tests

For this detection process, two individual tests were performed.

(i) Troponin I test: For the detection of MI (Myocardial infarction), Troponin I test was performed. Serum sample was collected & "Getin 110 Immunofluorescence Quantitative Analyzer" was used for this test. The detection method is Immunofluorescence Assay (IFA). Here the reference range of Troponin I is: < 0.10 ng/ml (Stein *et al*, 2008).

(ii) ECG (Electrocardiogram): To detect MI by ECG Mindray BeneHeart R12 ECG machine was used.

Statistical analysis

To carry out the second part of the experiment, demographic characteristics, diabetes related test were analyzed by Student's t-test. The comparison between the diabetes and progression of kidney and heart disease due to microalbuminuria were done by R programming. And the correlation of microalbuminuria with heart disease and renal disorder were done by ANOVA and Pearson correlation coefficient respectively.

3. RESULTS

General subject characteristics

A total of 149 patients with minimum of 5 years of type 2 Diabetes mellitus individuals were included in the present study. The prevalence of microalbuminuria in this study was 38%. The demographic and clinical characteristics of the subjects are shown in Table 1.

Table 1. Comparison of clinical and biological parameters occurred during type 2 diabetic patients (n=149)

	Normoalbuminuria (n=92)		**Microalbuminuria** (n=57)		P
	Lower	Upper	Lower	Upper	
Age, in years	49.1070	53.8060	52.4461	58.1855	0.4090
Body mass index, BMI, in kg/m^2	23.8796	25.0589	23.2951	24.8418	0.0920
Duration, in years	8.7178	11.2169	10.0353	13.4384	0.0420
Blood pressure					
Systolic blood pressure, mmHg	128.7727	134.7056	133.6602	142.8310	0.1560
Diastolic blood pressure, mmHg	81.5888	84.7155	84.2252	88.4063	0.7550
Diabetes related tests					
FBS (Fasting Blood sugars)	9.9127	11.6567	10.5609	13.1841	0.9880
RBS (Random blood sugars)	8.0741	19.2116	10.2665	15.5451	0.0140
2hABF (Two hours after breakfast Test)	14.7253	17.3380	14.2534	17.7769	0.0160

Comparison between the patients of normoalbuminuria and microalbuminuria in their respective duration of diabetes

The number of patients of normoalbuminuria were 16 in 5 years of diabetes, 11 in 6 years of diabetes, 12 in 7 years of diabetes, 12 in 8 years of diabetes, 4 in 9 years of diabetes, 11 in 10 years of diabetes, 4 in 12 years of diabetes, 0 in 13 years of diabetes, 1 in 14 years of diabetes, 5 in 15 years of diabetes, 1 in 16 years of diabetes, 2 in 18 years of diabetes, 3 in 20 years of diabetes, 1 in 22 years of diabetes, 1 in 25 years of diabetes, 2 in 28 years of diabetes, 2 in 30 years of diabetes, 0 in 35 years of diabetes. On the other hand, the number of patients of microalbuminuria were 12 in 5 years of diabetes, 6 in 6 years of diabetes, 5 in 7 years of diabetes, 3 in 8 years of diabetes, 1 in 9 years of diabetes, 5 in 10 years of diabetes, 4 in 12 years of diabetes, 3 in 13 years of diabetes, 5 in 14 years of diabetes, 1 in 16 years of diabetes, 2 in 18 years of diabetes, 3 in 20 years of diabetes, 1 in 22 years of diabetes, 1 in 25 years of diabetes, 2 in 28 years of diabetes, 2 in 30 years of diabetes and 1 in 35 years of diabetes (Figure 1).

Comparison of normoalbuminuria and microalbuminuria in kidney diseases

The analysis of kidney disease of diabetes mellitus was done through measuring creatinine. It was split into four parts. One part was normoalbuminuria with normal creatinine range, second one was normoalbuminuria with increased creatinine level, third one was microalbuminuria with normal creatinine level and the fourth one was microalbuminuria with increased creatinine level.

For the first condition which was normoalbuminuria with normal creatinine level, the number of patients were 11 in 5 years of diabetes, 8 in 6 years of diabetes, 7 in 7 years of diabetes, 6 in 8 years of diabetes, 2 in 9 years of diabetes, 7 in 10 years of diabetes, 1 in 12 years of diabetes, 1 in 18 years of diabetes, 1 in 20 years of diabetes (Figure 2).

For the second condition which was normoalbuminuria with increased creatinine level, the number of patients were 8 in 5 years of diabetes, 3 in 6 years of diabetes, 4 in 7 years of diabetes, 6 in 8 years of diabetes, 2 in 9 years of diabetes, 4 in 10 years of diabetes, 3 in 12 years of diabetes, 1 in 14 years of diabetes, 5 in 15 years of diabetes, 1 in 16 years of diabetes, 2 in 18 years of diabetes, 2 in 20 years of diabetes, 1 in 22 years of diabetes, 1 in 25 years of diabetes, 2 in 28 years of diabetes, 2 in 30 years of diabetes (Figure 3).

For the third condition which was microalbuminuria with normal creatinine level, the number of patients were 3 in 5 years of diabetes, 3 in 6 years of diabetes, 3 in 7 years of diabetes, 2 in 8 years of diabetes, 1 in 9 years of diabetes, 1 in 10 years of diabetes,

1 in 12 years of diabetes, 1 in 13 years of diabetes, 1 in 14 years of diabetes, 1 in 15 years of diabetes, 1 in 30 years of diabetes (Figure 4).

For the fourth condition which was microalbuminuria with increased creatinine level, the number of patients were 6 in 5 years of diabetes, 3 in 6 years of diabetes, 3 in 7 years of diabetes, 1 in 8 years of diabetes, 4 in 10 years of diabetes, 3 in 12 years of diabetes, 2 in 13 years of diabetes, 4 in 14 years of diabetes, 3 in 15 years of diabetes, 1 in 16 years of diabetes, 2 in 17 years of diabetes, 4 in 20 years of diabetes, 1 in 25 years of diabetes, 1 in 35 years of diabetes (Figure 5).

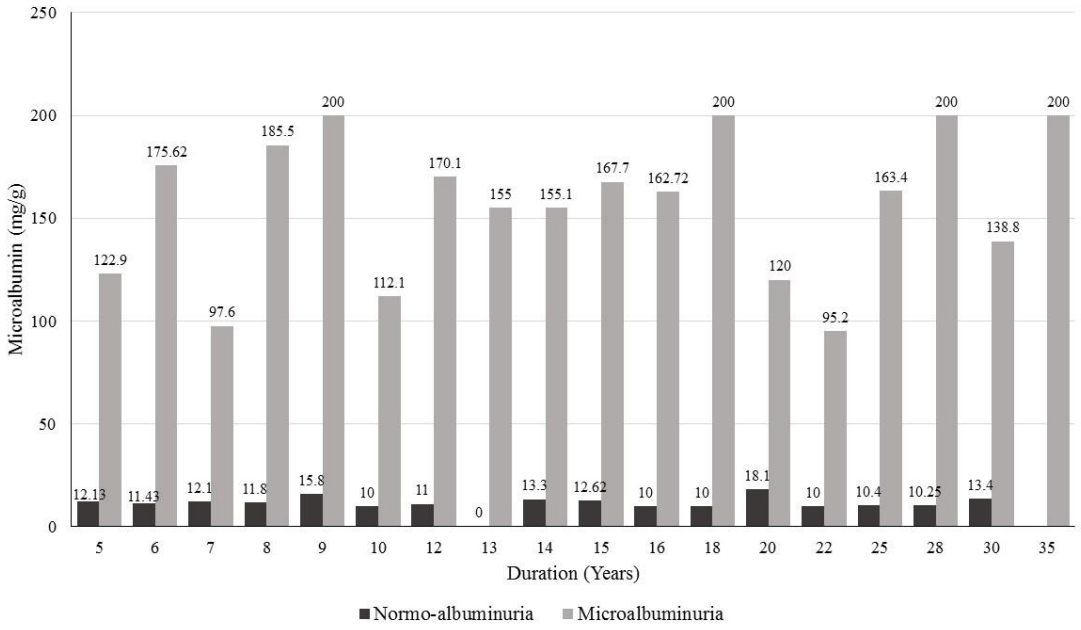

Figure 1: Comparison of the patients of normoalbuminuria and microalbuminuria in their respective duration of diabetes.

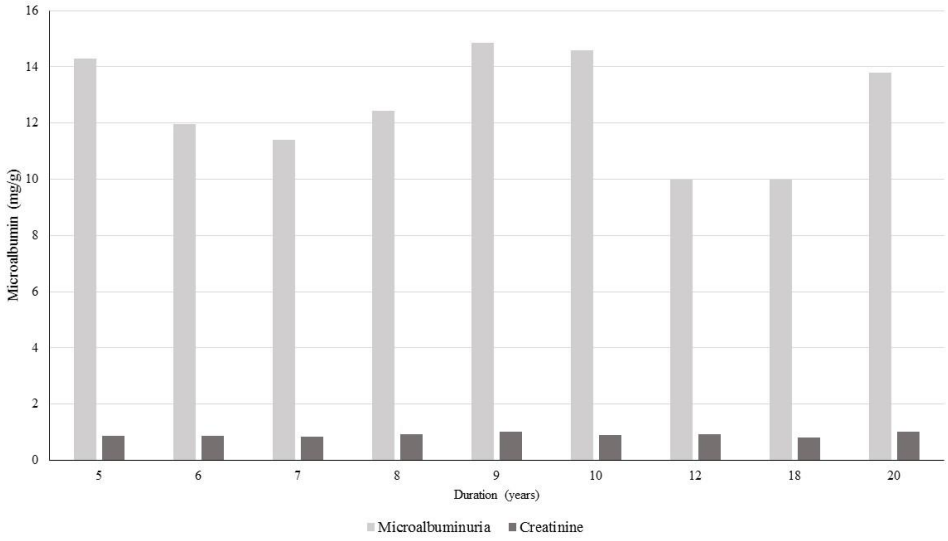

Figure 2: Occurrence of normal creatinine level in normoalbuminuria patients

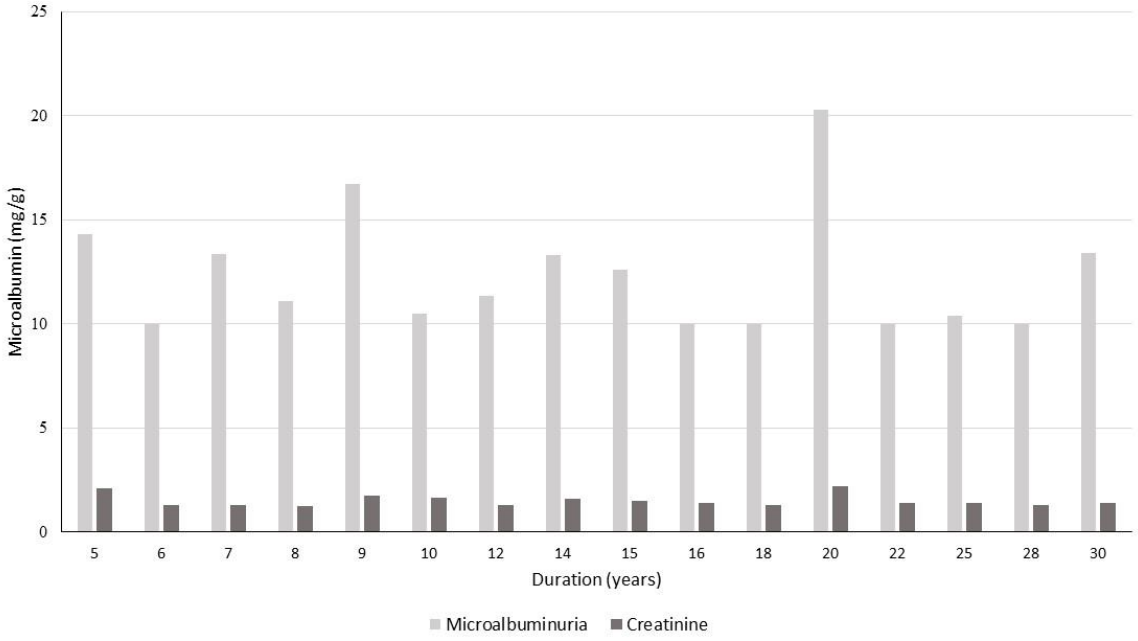

Figure 3: Occurrence of increased level of creatinine in normoalbuminuria patients.

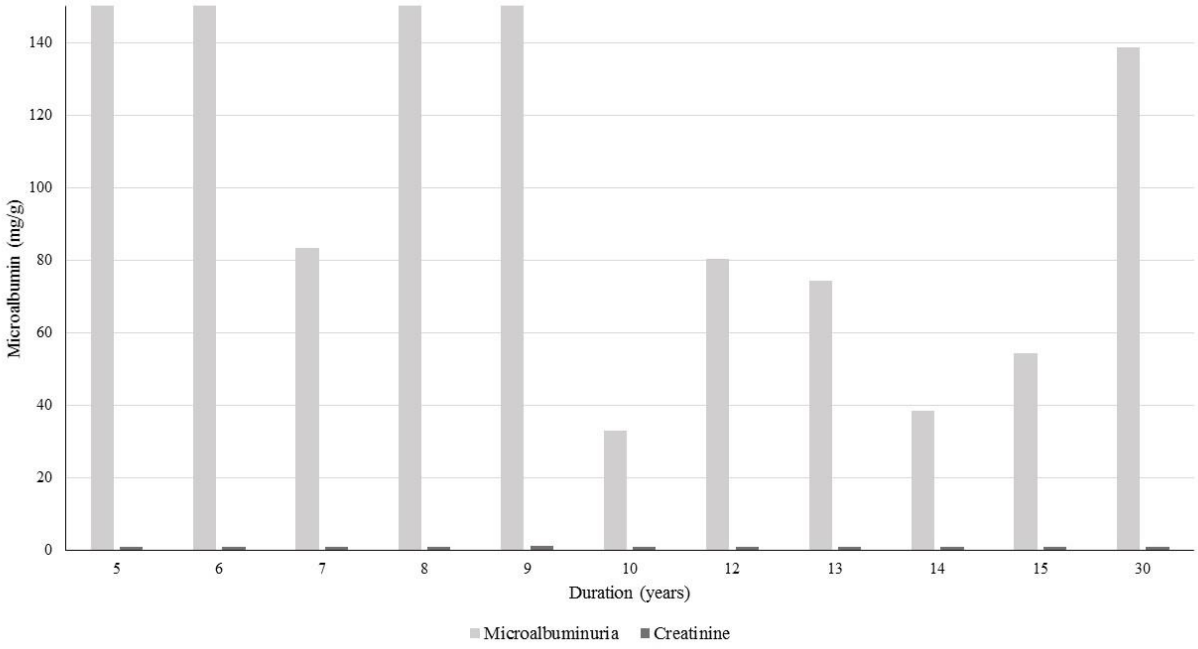

Figure 4 : Occurrence of normal level of creatinine in microalbuminuria patients

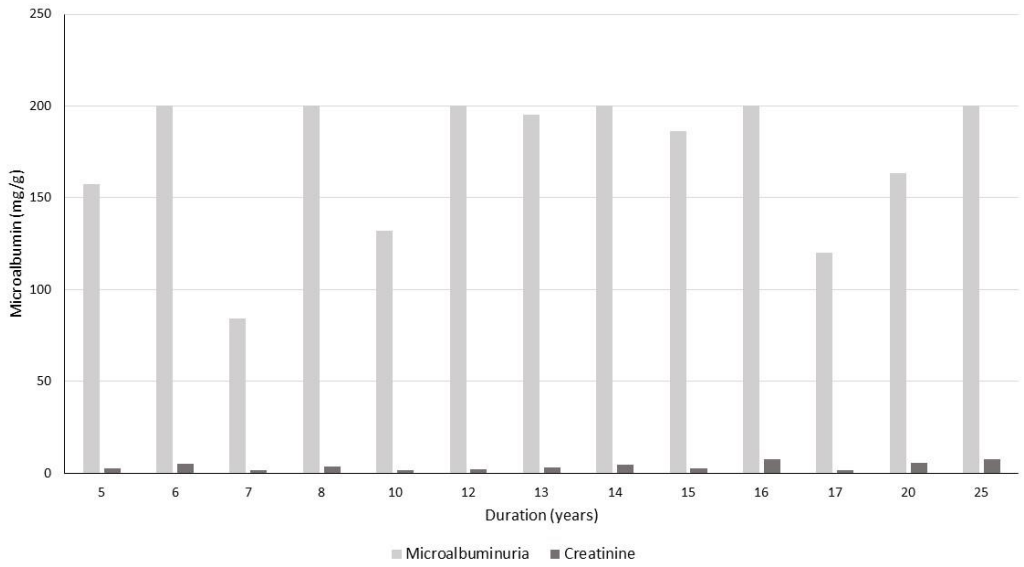

Figure 5: Occurrence of increased level of creatinine in microalbuminuria patients

Correlation of normoalbuminuria and microalbuminuria with kidney disease

The Pearson correlation coefficient, *r*, can accept a range of values from +1 to -1. A value of 0 specifies no association between the two variables whereas a value greater than 0 shows a positive association; that means, if the value of one variable rises, the other variable value also rises. While, a value less than 0 dictates a negative association between variables; that means, if the value of one variable increases, the other variable value decreases. Since the Pearson coefficient value is 0.487 (Table 2), so it can be said that the result is significant. That means there is a positive relation of microalbuminuria and creatinine that contributes to the progression of kidney disease (Figure 6).

Table 2 Correlation of normoalbuminuria and microalbuminuria with kidney disease

		Microalbuminuria	Creatinine
Microalbuminuria	Pearson Correlation	1	.487**
	N	149	149

Comparison of normoalbuminuria and microalbuminuria in heart disease (Troponine I and ECG)

The analysis of heart disease of diabetes mellitus was done through measuring troponine I and ECG. It was split into four parts. One part was normoalbuminuria with negative Troponine I and normal ECG, second one was normoalbuminuria with positive Troponine I and abnormal ECG, third one was microalbuminuria with negative Troponine I and normal ECG and the fourth one was microalbuminuria with positive Troponine I and abnormal ECG.

For the first condition which was normoalbuminuria with negative Troponine I and normal ECG, the number of patients were 16 in 5 years of diabetes, 11 in 6 years of diabetes, 10 in 7 years of diabetes, 11 in 8 years of diabetes, 3 in 9 years of diabetes, 10 in 10 years of diabetes, 4 in 12 years of diabetes, 1 in 14 years of diabetes, 4 in 15 years of diabetes, 1 in 16 years of diabetes, 3 in 18 years of diabetes, 3 in 20 years of diabetes, 1 in 22 years of diabetes, 1 in 25 years of diabetes, 1 in 28 years of diabetes, 1 in 30 years of diabetes (Figure 7).

For the second condition which was normoalbuminuria with positive Troponine I and abnormal ECG, the number of patients were 1 in 5 years of diabetes, 2 in 7 years of diabetes, 1 in 8 years of diabetes, 1 in 9 years of diabetes, 1 in 10 years of diabetes, 3 in 12 years of diabetes, 1 in 15 years of diabetes, 1 in 28 years of diabetes (Figure 8).

For the third condition which was microalbuminuria with negative Troponine I and normal ECG, the number of patients were 9 in 5 years of diabetes, 6 in 6 years of diabetes, 4 in 7 years of diabetes, 1 in 8 years of diabetes, 1 in 9 years of diabetes, 1 in 10 years of diabetes, 4 in 12 years of diabetes, 3 in 13 years of diabetes, 3 in 20 years of diabetes, 1 in 30 years of diabetes (Figure 9).

For the fourth condition which was microalbuminuria with positive Troponine I and abnormal ECG, the number of patients were 2 in 5 years of diabetes, 1 in 7 years of diabetes, 2 in 8 years of diabetes, 2 in 15 years of diabetes, 1 in 17 years of diabetes, 1 in 20 years of diabetes, 1 in 25 years of diabetes (Figure 10).

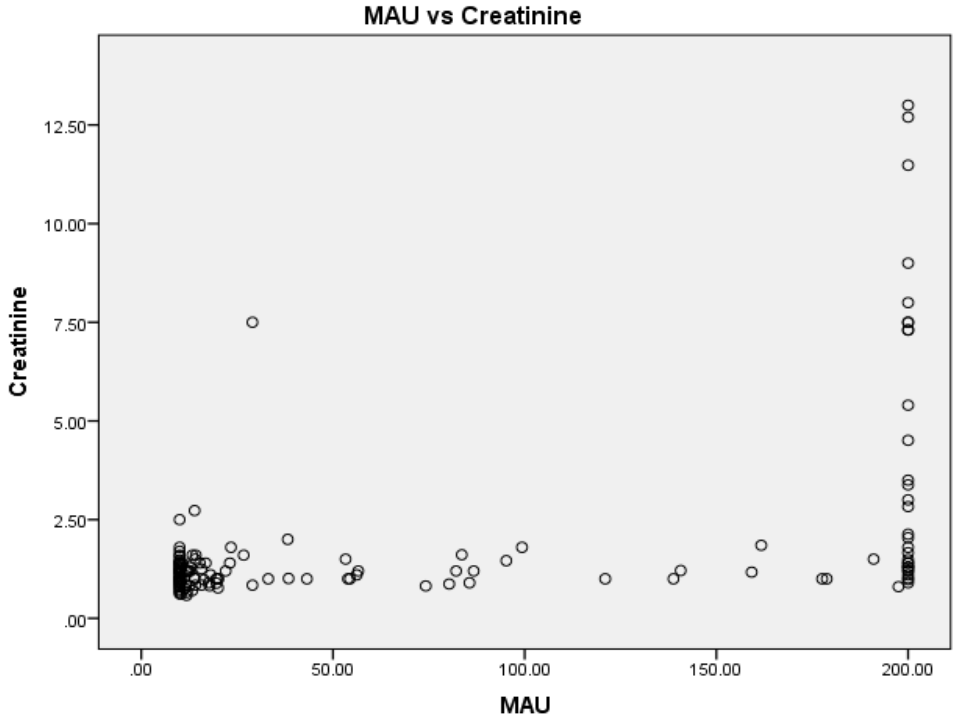

Figure 6: Correlation of normoalbuminuria and microalbuminuria with kidney disease

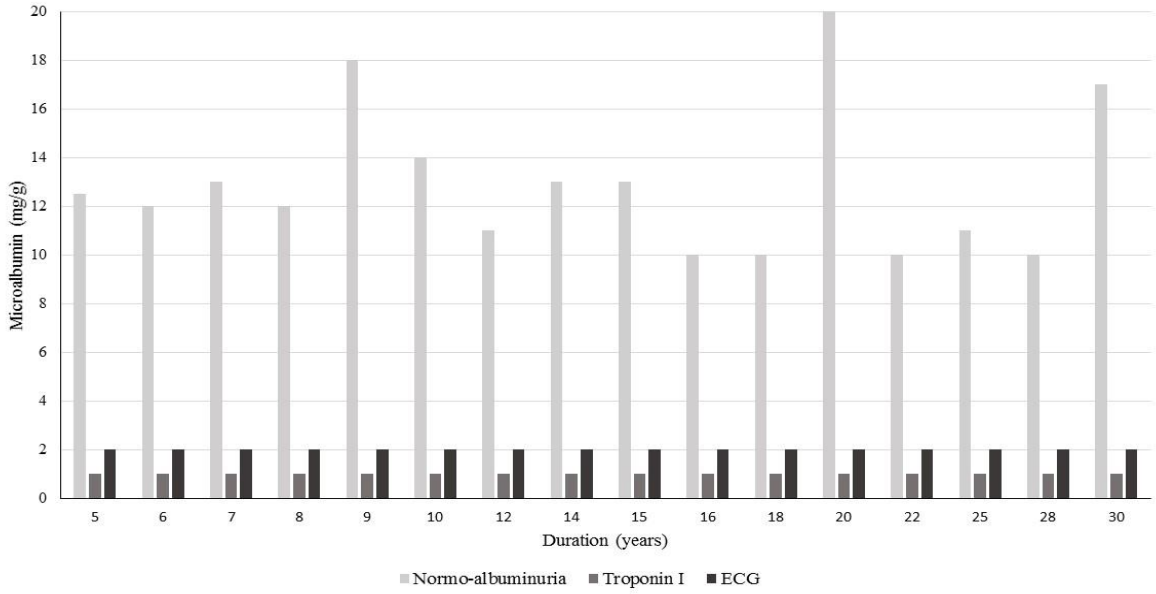

Figure 7: Occurrence of negative Troponine I and normal ECG in normoalbuminuria patients.

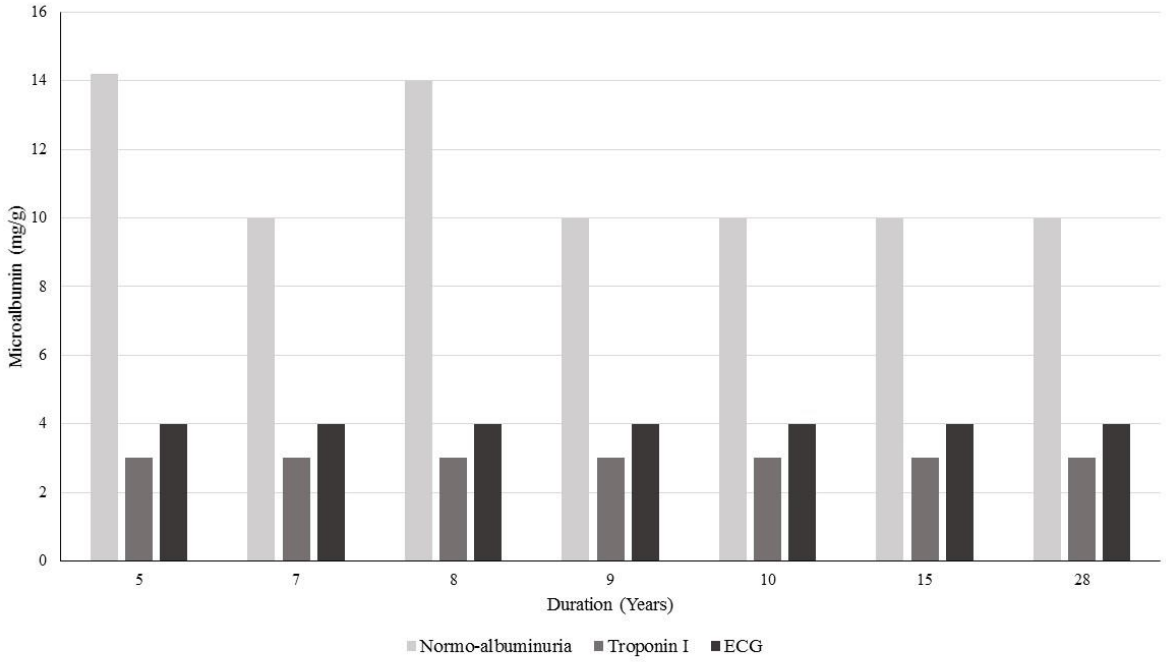

Figure 8: Occurrence of positive Troponine I and abnormal ECG in normoalbuminuria patients.

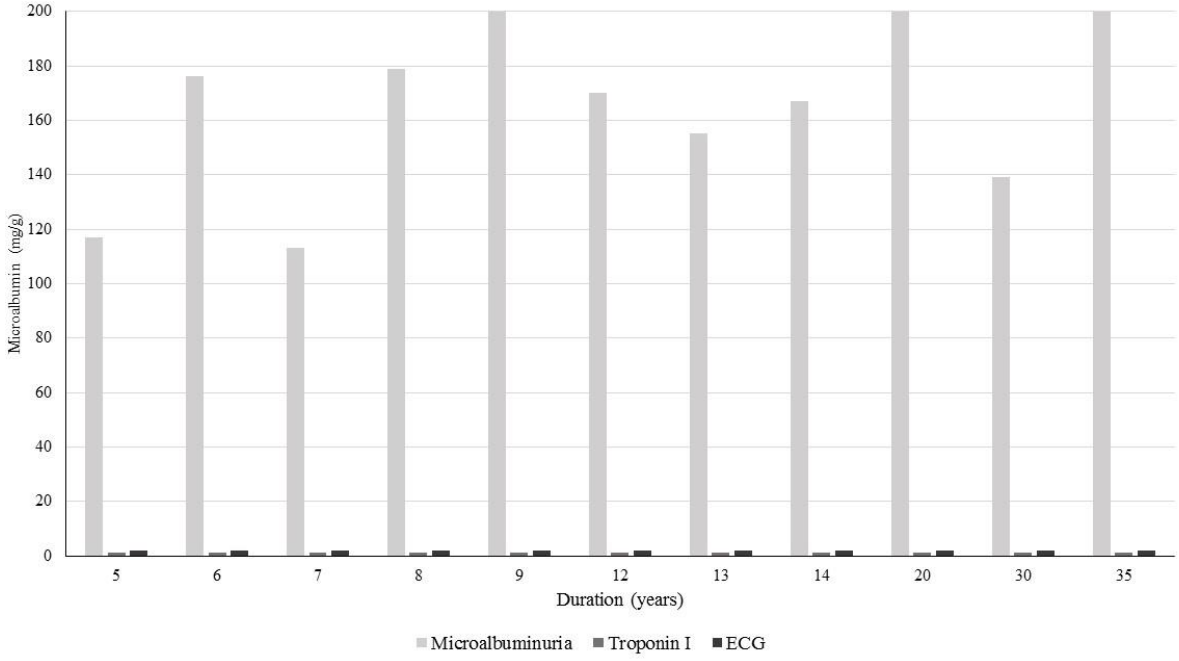

Figure 9: Occurrence of negative Troponine I and normal ECG in microalbuminuria patients.

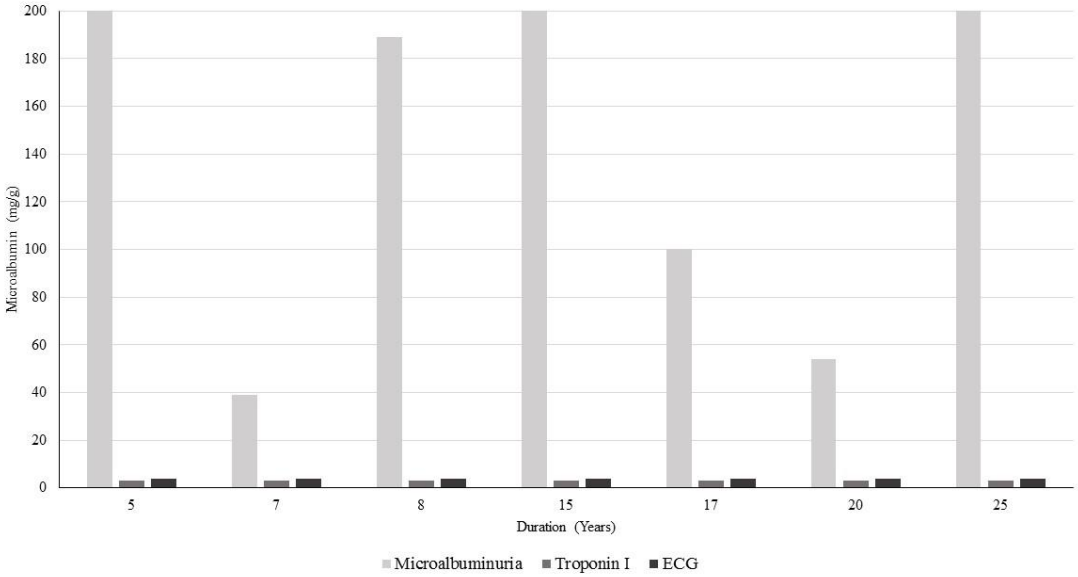

Figure 10: Occurrence of positive Troponine I and abnormal ECG in microalbuminuria patients.

Correlation of microalbuminuria with heart disease in diabetes patients

From the result of Table 3, it can be said that there is a positive correlation between microalbuminuria and troponine I. So, it can be said that microalbumin can contribute to heart disease.

From the result of Table 4, it can be said that there is a positive correlation between microalbuminuria and ECG. So, it can be said that microalbumin can contribute to heart disease.

Table 3: Correlation between microalbuminuria and troponine I

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	25916.957	1	25916.957		
Within Groups	890543.312	148	6058.118	4.278	.040
Total	916460.269	149			

Table 4: Correlation between microalbuminuria and ECG

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	29690.008	1	29690.008		
Within Groups	886770.261	148	6032.451	4.922	.028
Total	916460.269	149			

4. DISCUSSION

In this study, a cross-sectional association of microalbuminuria with cardiovascular and kidney disease progression was found in type 2 Diabetes Mellitus in Bangladeshi population. On the contrary, some of the represented results concerning the prevalence and association of microalbuminuria with different parameters in type-2 diabetes mellitus yielded some variations from the other studies because of the chosen cut off value, patient selection, and more importantly duration of diabetes and of prior treatment (American Diabetes Association, 2003).

A prevalence of microalbuminuria of 38% was found in a cohort of 149 patients which is consistent with the three previous studies on the onset of type 2 diabetic subjects of Bangladeshi population (Islam, 1993; Alam, 1995; Hada, 1998). But analysis of the

population found no statistically significant linear relationship of microalbuminuria with age and BMI which is contrary to the earlier studies that had shown positive correlation of microalbuminuria with age and BMI of the patients (Ruilope and Segura, 2006; Metcalf *et al*, 1992).This may be due to the confounding variables like duration of diabetes and glycemic control that would have played a significant role in the occurrence of microalbuminuria. Moreover, no significant difference was found in case of blood pressure between diabetic normoalbuminuric and diabetic microalbuminuric subjects. Similar results were found by Hada and Iqbal in type 2 diabetic subjects in the similar population (Hada, 1998; Iqbal, 2000). In contrast to this, increased blood pressure has been reported in type 1 diabetic patients with microalbuminuria (Mogensen *et al*, 1992; Wiseman *et al*, 1984). But there is some controversy as to whether the elevated arterial pressure precedes the development of microalbuminuria in type 1 diabetes or it occurs after its development (Wiseman *et al*, 1990).

With respect to duration of diabetes mellitus, a positive correlation was found which is persistent with many previous reports. Duration of prolonged diabetes causes the accumulation of the end products of hyperglycemia-induced advanced glycosylation which act as a significant contributor in this regard (Jungmann *et al*, 2001; Mogensen *et al*, 2000; Levin *et al*, 2000).

In this study, to establish the association of microalbuminuria with kidney disease in type 2 diabetes mellitus, serum creatinine concentration was observed since it is widely considered as an imprecise index of renal function. A positive correlation of serum creatinine with microalbuminuria has been evident in this study. In a meta-analysis of 13 studies with more than 21,000 patients with chronic kidney disease, observed that the risk of end-stage renal disease was three times higher in those with albuminuria (Astor *et al*, 2011). They also found that as albuminuria increased, so did the risk of progression of chronic kidney disease and the incidence of acute kidney injury (Gansevoort *et al*, 2011). In addition, microalbuminuria predicts the development of overt diabetic nephropathy in type 1 and 2 diabetes; however, the relationship in type 2 diabetes is ambiguous due to the higher heterogeneity of this condition and the presence of other risk factors for microalbuminuria in these, specially elderly patients (Adler *et al*, 2003). Microalbuminuria invariably leads to overt diabetic nephropathy, and even though microalbuminuria may regress in most of the cases spontaneously, still it is the well-established predictor for increased risk of developing diabetic nephropathy in both type 1 and type 2 diabetes (Parving *et al*, 2002).

Furthermore, to investigate the relation of microalbuminuria with cardiovascular diseases in type 2 diabetic patients, Troponine I and ECG were considered as cardiac disease marker in the present study. In our study, Troponine I and ECG has shown positive correlation with microalbuminuria suggesting the association of microalbuminuria with clinical cardiovascular diseases. This finding is compatible with a systematic review by Dinneen and Gerstein that indicated microalbuminuria in type 2 diabetes patients was associated with a 2.4-fold increased risk for cardiovascular death compared to normoalbuminuria (Dinneen and Gerstein, 1997).There is an increasing body of evidence that microalbuminuria is a strong risk marker for cardiovascular disease. Results from the Framingham study demonstrated that proteinuria is associated with cardiovascular risk in the general population (Kannel *et al*, 1984). The Steno hypothesis suggests that microalbuminuria is an independent risk marker of diabetic microangiopathy and macroangiopathy (Deckert *et al*, 1989). In addition, it has been proposed that microalbuminuria is simply a marker of generalized atherosclerosis which explains its association with clinical cardiovascular diseases (Jager *et al*, 1999).

5. CONCLUSION

Our study adds novel evidence on a prospective association of microalbuminuria with cardiovascular and renal disorder. However, due to small sample size and not based on the general population, selection bias might have affected the outcome of the study. Therefore, further well-designed and powerful epidemiological studies with large sample size are necessary to confirm the results of the study. Ultimately, these results emphasize the need for additional studies which will extend the concept that suppressing microalbuminuria should be evaluated further as a goal of therapy to achieve optimal cardiovascular and renal protection in individual patient with type 2 diabetes mellitus.

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Authors' Contribution

Fahmida Sultana Rima supervised the study and participated in its design and coordination and helped to draft the manuscript. Tahsin Nairuz participated in drafting the manuscript. Sajib Hossain collected all the data and samples. Aliraj Kanon and Tasnim Islam helped in those techniques. Dr. Richard Malo carried out some clinical tests. Dr. Asim Chakrabarty participated in giving the ideas.

Potential conflict of interests

Authors declared no potential conflict of authorship.

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